Behavioral/Systems/Cognitive

Aversion-Related Circuitry in the Cerebellum: Responses to Noxious Heat and Unpleasant Images

Eric A. Moulton,[1]* Igor Elman,[2]* Gautam Pendse,[1] Jeremy Schmahmann,[3] Lino Becerra,[1] and David Borsook[1]

[1]Pain/Analgesia Imaging Neuroscience (P.A.I.N.) Group and [2]Clinical Psychopathology Laboratory, McLean Hospital, Harvard Medical School, Belmont, Massachusetts 02478, and [3]Ataxia Unit, Cognitive Behavioral Neurology Unit, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114

The cerebellum is reliably activated during both acute and chronic pain conditions, but it is unclear whether the response to aversive painful stimuli can be generalized to other aversive stimuli. We hypothesized that cerebellar activation during pain reflects higher-level encoding of aversive stimuli. We used functional magnetic resonance imaging (fMRI) to compare cerebellar responses in 11 healthy volunteers to noxious heat (46°C) applied to the hand and to the passive viewing of images selected from the International Affective Picture System. Aversive stimuli in the form of noxious heat and unpleasant pictures (unpleasant vs neutral) activated overlapping areas in the posterior cerebellum, specifically in hemispheric lobule VI, Crus I, and VIIb. Pleasant pictures (pleasant vs neutral) did not share the same pattern of activation as observed with the aversive stimuli. Cerebellar areas that showed functional overlap with both heat pain and unpleasant picture viewing were significantly inversely correlated with fMRI signals measured in limbic system structures, including the anterior hypothalamus, subgenual anterior cingulate cortex, and the parahippocampal gyrus. Heat-specific functional connectivity was detected in many regions including primary motor cortex, secondary somatosensory cortex, anterior insula, and the periaqueductal gray. The overlap between cerebellar lobuli reactive to noxious heat and passive viewing of unpleasant images suggest that the cerebellum may contain specific regions involved in encoding generalized aversive processing. The separate cortical networks suggest that noxious heat-evoked responses in the cerebellum can be divided into sensorimotor and emotional networks.

Introduction

Cerebellar activity is often detected in neuroimaging studies of pain (Moulton et al., 2010) and other studies evaluating emotional processing (Fusar-Poli et al., 2009), even in the absence of a motor task. While the role of the cerebellum in non-motor and cognitive function has been gaining prominence (Stoodley and Schmahmann, 2009; Strick et al., 2009), its functional relevance during pain processing is still frequently attributed to motor processing. Pain is a multidimensional experience that includes sensory, affective, and cognitive components, and cerebellar activation could relate to any combination of these constructs. In support of this concept, prior studies have indicated that the cerebellum is involved in generalized emotional perception (Murphy et al., 2003; Konarski et al., 2005), including aversive picture perception (Lane et al., 1997; Paradiso et al., 1999; Bermpohl et al., 2006). Together, the data show that a generalized "aversive" response in cerebellar function may reflect an important role in modality-nonspecific encoding of aversive stimuli. Thus far, no studies have directly compared cerebellar responses to aversive thermal stimuli versus aversive pictures.

Human pain imaging studies often detect cerebellar activation, most frequently in the anterior vermis and posterior hemispheres (Moulton et al., 2010). Although not every study has commented on the significance of cerebellar activation during pain, a common interpretation relates to motor control of withdraw behavior (Peyron et al., 2000). Non-motor interpretations have also been proposed, including attention (Casey et al., 1996), rehearsal of verbal rating (Casey et al., 1996), and memory processes related to learning (Ploghaus et al., 2000). The idea that the cerebellar processing may be more directly related to pain and nociceptive modulation has recently been gaining traction (Bingel et al., 2002; Helmchen et al., 2003; Strigo et al., 2003; Borsook et al., 2008; Yelle et al., 2009). These interpretations were made primarily in the singular context of pain-related activation, and a multimodal approach using two different aversive stimuli in the same cohort of individuals may yield additional insight into the functional relevance of the cerebellum during pain.

Cerebellar activation in the posterior hemispheres has also been detected in neuroimaging studies of emotion (Fusar-Poli et al., 2009; Stoodley and Schmahmann, 2009), particularly in studies using emotionally evocative pictures. Unpleasant and neutral pictures, drawn from the International Affective Picture System (IAPS), can produce differential cerebellar responses (Lane et al., 1997; Paradiso et al., 1999; Bermpohl et al., 2006). The possibility that pain and emotional processing may share a substrate in the cerebellum has not yet been evaluated.

Received Dec. 22, 2010; accepted Jan. 23, 2011.

This work was supported by the National Institutes of Health (National Institute on Drug Abuse Grant K01DA024289 to E.A.M. and Grant R01DA017959 to I.E.; and National Institute of Neurological Disorders and Stroke Grant K24NS064050 to D.B.), and the Birmingham and MINDlink Foundations (J.S.). We acknowledge Susie Morris, Sadie Cole, and Won Chi for their assistance in subject recruitment and data collection.

*E.A.M. and I.E. contributed equally to this work.

Correspondence should be addressed to Dr. Eric A. Moulton, P.A.I.N. Group, McLean Hospital, 115 Mill Street, Belmont, MA 02478. E-mail: emoulton@mclean.harvard.edu.

DOI:10.1523/JNEUROSCI.6709-10.2011

 0270-6474/11/313795-10$15.00/0

We hypothesized that cerebellar activation during pain reflects higher-level encoding of aversive stimuli. To test this proposition, we compared cerebellar responses to noxious contact heat and the passive viewing of pictures from the IAPS using functional magnetic resonance imaging (fMRI). If noxious heat activates the same cerebellar regions as aversive pictures, this would suggest the presence of multimodal aversion-specific cerebellar circuitry.

Materials and Methods

Subjects

Eleven healthy right-handed subjects (6 males, 5 females) were recruited by advertisement and participated in this study after providing written informed consent to participate in this experiment. The study was approved by the McLean Hospital Institutional Review Board, and met the scientific and ethical guidelines for human pain research of the Helsinki Accord and the International Association for the Study of Pain. The subjects averaged 39 ± 10 years in age, and had no psychiatric history as determined by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Text Revision (American Psychiatric Association, 2000). Recent drug and alcohol consumption was ruled out by negative results on the urine toxicology screen and breathalyzer. All subjects were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971) and in good physical health as determined by the Cornell Medical Index Health Questionnaire (Seymour, 1976). Subjects' pain free status was ascertained via the Short Form version of the Brief Pain Inventory (Anderson et al., 2001).

Thermal stimulation

Thermal stimuli were delivered to the dorsum of the left hand using a 3 × 3 cm contact thermode (TSA-II, Medoc Advanced Medical Systems). At rest, the thermode maintained a steady baseline temperature of 32°C. At a rate of 4°C/s, the probe surface was heated to 46°C, which was maintained for 15 s. The temperature returned to the baseline at a rate of 4°C/s to end the stimulus event. The interstimulus interval was 30 s.

Visual stimulation

Visual stimuli consisted of 300 pictures selected from the IAPS, developed by the National Institute of Mental Health Center for Emotion and Attention at the University of Florida (Lang et al., 2008). The IAPS features color photographs that depict scenes with varying ability to evoke emotional responses. The subject of these pictures can range from abstract art to graphic mutilation to erotica. Pictures were sorted into "pleasant," "neutral," and "unpleasant" categories based on the numeric rating scales used to collect the normative ratings for the intensity of the affective valence and arousal as previously reported (Lang et al., 2008). The dimension of valence intensity ranges from unpleasant (1) to pleasant (9), while arousal ranges from calm (1) to excited (9). Pleasant pictures were sorted and selected from the 956 available IAPS pictures in two steps: (1) selecting the 120 pictures with the highest normative valence intensity scores, and (2) from this subset, selecting the 90 pictures with the highest normative arousal scores. Unpleasant pictures were sorted similarly: (1) selecting the 120 pictures with the lowest normative valence scores, and (2) from this subset, selecting the 90 pictures with the highest normative arousal scores. Neutral pictures were selected by: (1) identifying pictures with normative valence scores between 4.5 and 5.5, and (2) from this subset, selecting the 120 pictures with the highest normative arousal scores. Visual stimuli were presented in blocks of 10 sequential IAPS pictures for each of the three categories of images. Each Pleasant, Unpleasant, or Neutral block was presented for 22 s, with 30 s of rest (black fixation cross on a white background) separating blocks.

Scanning experimental paradigm

Each subject underwent a single scanning session, which included one fMRI scan for noxious heat stimulation at 46°C (Heat-46), and three scans for IAPS picture presentation. The fMRI scan with thermal stimuli consisted of a 55 s baseline period followed by three stimulus cycles, as described above. During each thermal stimulus, subjects rated pain intensity and unpleasantness for each stimulus using a rating dial in their right hand to manipulate an online visual analog scale (VAS) presented using the software package LabVIEW 5.1 (National Instruments Corp.). Thus, subjects made their ratings using the hand opposite to the hand being stimulated, so as to potentially segregate activity due to sensory versus motor events. The VAS for pain intensity was scaled from "No Pain" (0) to "Max Pain" (10), and unpleasantness was scaled from "Min" (0) to "Max" (10). Pain ratings for two subjects were lost due to a technical error. Each of the three fMRI scans with IAPS pictures consisted of a 62 s baseline followed by 10 visual stimulation blocks presented in pseudorandom order: three blocks of Pleasant pictures, three blocks of Unpleasant pictures, and four blocks of Neutral pictures. A subject was never presented with the same picture more than once. After the completion of each IAPS fMRI scan, using the same scale as used in the generation of the normative IAPS ratings (1–9, as described above), subjects made two verbal ratings of valence: the average valence experienced for the (1) Pleasant and (2) Unpleasant blocks.

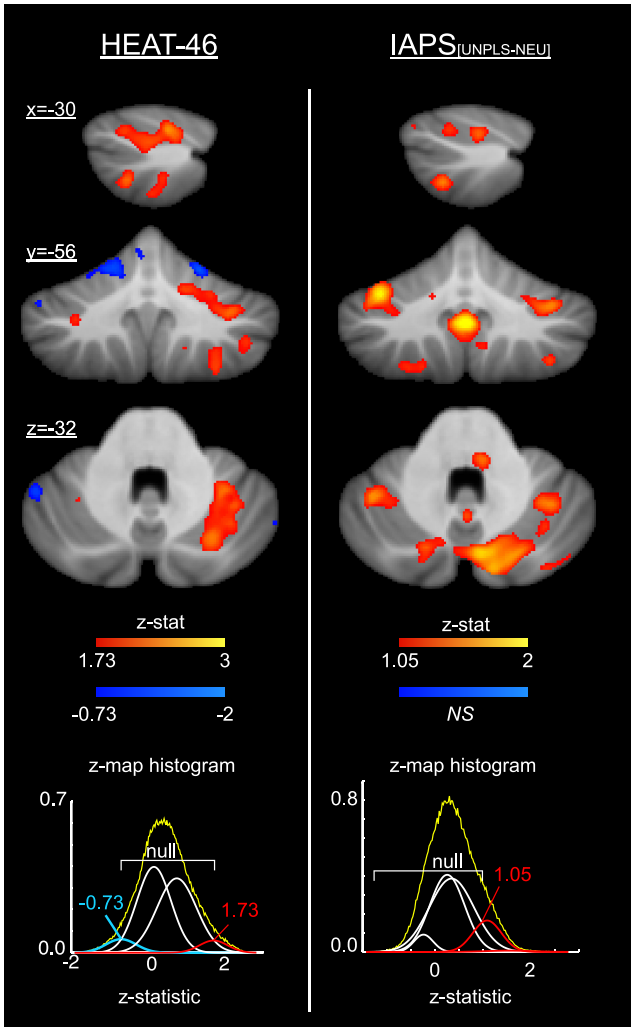

Figure 1. Cerebellar responses to noxious heat and Unpleasant-Neutral pictures. The statistical maps overlay the SUIT atlas (Diedrichsen, 2006), and the coordinates displayed correspond to the standard MNI152 atlas. For coronal and axial images, the left cerebellar hemisphere corresponds with the right side of the image. Activation and deactivation maps were thresholded at a posterior probability of $p > 0.5$ using GMM. Statistical maps have been spatially smoothed using a median filter for display purposes. *Z*-map histograms show the positive (red) and negative (blue) distributions relative to the null distribution (white) identified by Gaussian mixture modeling of the *z*-statistic histograms (yellow) for each activation map. The colored numbers indicate the *z*-statistic thresholds determined by differentiation of positive and negative distributions from the null. A negative distribution could not be statistically differentiated from the null distribution for the Unpleasant-Neutral condition.

Table 1. Cerebellar responses to noxious heat

Cluster	Max ROI	MNI (z_{max})			Max *z*-stat	Vol (cm^3)	Composition
		x	*y*	*z*			
46°C— Positive ($z > 1.73$)							
Cerebellum							
1	L VIIIa	−18	−68	−55	2.83	2.39	47% L VIIb; 39% L VIIIa; 8% L VIIIb; 7% L CrII
2	L VI	−29	−52	−30	2.54	0.79	96% L VI; 3% L CrI
3	L V	−16	−53	−23	2.45	0.62	42% L V; 34% L VI
4	L CrI	−25	−68	−35	2.44	1.08	56% L CrI; 23% L VI; 1% L CrII
5	L CrI	−34	−56	−33	2.34	0.80	64% L CrI; 16% L VI
6	R VI	34	−50	−35	2.24	0.35	33% R VI; 28% R CrI
7	L VIIIa	−27	−54	−52	2.15	0.46	97% L VIIIa; 2% L VIIIb
8	L CrII	−41	−56	−46	2.03	0.35	71% L CrII; 24% L VIIb
Brainstem							
1	Mid	5	−24	3	2.00	0.41	
46°C—Negative ($z < -0.73$)							
Cerebellum							
1	R VI	30	−47	−23	−1.93	4.62	40% R V; 28% R VI; 20% R I-IV
2	R IX	7	−50	−46	−1.57	0.37	88% R IX
3	L VI	−20	−58	−15	−1.41	0.69	67% L VI; 5% L V

Thresholds were determined using Gaussian mixture modeling (Pendse et al., 2009). Cerebellar regions were identified using the SUIT probabilistic atlas of the human cerebellum (Diedrichsen et al., 2009). Minimum 7 voxels in acquired space (0.30 cm^3). L, Left; R, right; CrI, Crus I; CrII, Crus II; Mid, midbrain.

Table 2. Differential cerebellar responses to unpleasant and neutral images by contrast analysis: IAPS, Unpls > Neu ($z > 1.05$)

Cluster	Max ROI	MNI (z_{max})			Max *z*-stat	Vol (cm^3)	Composition
		x	*y*	*z*			
Cerebellum							
1	R VI	39	−51	−26	2.79	3.61	48% R VI; 45% R CrI
2	V IX	1	−57	−38	2.19	12.80	25% L CrII; 14% L CrI; 12% L VIIb; 6% Vermis VI; 5% V IX; 5%L IX; 4% L VI; 4% R IX; 4% Vermis VIIIa; 4% R CrI; 3% R VI; 3% Vermis CrII; 2% Vermis VIIIb
3	L CrI	−34	−66	−29	1.67	0.60	86% L CrI; 13% L VI
4	L CrI	−36	−55	−31	1.64	0.92	64% L VI; 36% L CrI
5	L CrI	−38	−80	−29	1.59	0.44	93% L CrI
6	R VIIIb	17	−61	−56	1.41	0.41	56% R VIIIb; 44% R VIIIa
Brainstem							
1	Mid	2	−28	−4	1.75	0.53	
		−2	−18	−4	1.56	1.33	
		7	−30	−13	1.55	0.39	
		−10	−28	−12	1.53	0.41	
	D Med	−5	−36	−31	1.53	0.46	

Thresholds were determined using Gaussian mixture modeling (Pendse et al., 2009). Cerebellar regions were identified using the SUIT probabilistic atlas of the human cerebellum (Diedrichsen et al., 2009). Minimum 7 voxels in acquired space (0.30 cm^3). L, Left; R, right; CrI, Crus I; CrII, Crus II; D Med, dorsal medulla; Mid, midbrain.

Image acquisition and analysis

Image acquisition. Subjects were scanned in a 3T Siemens Trio MRI scanner using a circularly polarized head coil. Anatomical images were acquired using a magnetization prepared rapid gradient echo sequence [128 slices 1.33 mm thick, with an in-plane resolution of 1 mm (256 × 256)]. Functional scans were collected using an echo planar imaging sequence (echo time/repetition time (TE/TR) = 30/2500 ms for 46°C, TE/TR = 30/3000 ms for IAPS). Different repetition times were chosen to optimize the acquisition to the timing of the stimulus presentations. Both 46°C and IAPS functional scans consisted of 41 slices, with 3.5 mm isometric resolution, with the acquisition coronally oriented to the match the brainstem axis and included the cerebellum. Eighty-four volumes were captured for the 46°C fMRI scans (3:30), and 199 volumes were captured for the IAPS fMRI scans (9:57).

Individual subject-level image processing. Functional image datasets were processed and analyzed with FSL 4.1.5 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). Visual screening of the functional volumes revealed that none of the subjects showed indications of gross movement (>1 voxel). The initial two volumes were removed from each of the functional scans to allow for signal equilibration. The skull and other non-brain areas were extracted from the anatomical and functional scans using FSL's script brain extraction tool (BET). Motion Correction using FMRIB's Linear Image Registration Tool (MCFLIRT) was performed on each functional scan. All volumes were mean-based intensity normalized by the same factor. A 75 s high-pass temporal filter was applied for Heat-46 fMRI scans, while a 394 s high-pass filter was applied for IAPS fMRI scans.

First-level fMRI analysis of single-subject data was performed with FMRI Expert Analysis Tool (FEAT) using FMRIB's Improved Linear Model (FILM) Version 5.98 with local autocorrelation correction (Woolrich et al., 2001). For the Heat-46 scans, the temperature profiles recorded during scanning were rescaled from 0 to 1 and entered as explanatory variables (EVs), as were their temporal derivatives. For the IAPS scans, three sets of EVs were generated based on boxcar functions that corresponded with the visual presentation of the Pleasant, Unpleasant, and Neutral stimulus blocks, as well as their temporal derivatives. All

EVs were convolved with a gamma function incorporating a 3 s SD and a 6 s hemodynamic lag. For the IAPS scans, two contrasts were run: (1) Unpleasant-Neutral ($IAPS_{[UNPLS-NEU]}$); and (2) Pleasant-Neutral ($IAPS_{[PLS-NEU]}$). An additional fixed effects analysis for the three IAPS scans for each subject was run with FEAT, such that each subject had an average $IAPS_{[UNPLS-NEU]}$ contrast and $IAPS_{[PLS-NEU]}$ contrast. The resulting individual subject-level statistical maps from all FEAT analyses were coregistered with the subjects' anatomical images with FMRIB's Linear Image Registration Tool (FLIRT).

Group-level cerebellar image analysis. For group analysis, individual subject statistics in the cerebellum were registered to the Spatially Unbiased Infraorbital Template (SUIT Version 2.4) (Diedrichsen, 2006; Diedrichsen et al., 2009) using the suit-toolbox (www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm) in SPM8 (www.fil.ion.ucl.ac.uk/spm). Unlike standard whole-brain atlases, the SUIT atlas preserves the anatomical detail of the cerebellum and provides more accurate intersubject alignment (Diedrichsen, 2006). The cerebellum and brainstem in the anatomical scans for each subject were first isolated, and then spatially normalized to the SUIT atlas with nonlinear deformation as implemented in SPM8 (Ashburner and Friston, 1999). The nonlinear deformation maps generated were used to register individual subject-level statistical maps in anatomical space to the SUIT atlas. Statistical maps in SUIT-space were spatially smoothed with a 3.5 mm full-width at half-maximum filter. With the SUIT template serving as the standard coordinate-space, group activation maps for Heat-46, $IAPS_{[UNPLS-NEU]}$, and $IAPS_{[PLS-NEU]}$ were generated by FEAT using fMRIB's Local Analysis of Mixed Effects (FLAME).

Statistical thresholding. All group-level statistical maps were subjected to alternative hypothesis testing using Gaussian mixture modeling (GMM), to identify categories of activated and deactivated voxels (Pendse et al., 2009). GMM is a standard technique generally used for unsupervised classification of data into multiple categories, and is not encumbered by the problem of multiple comparisons. The distribution of z-statistic values was not centered at zero. Hence, instead of basing inference on a fixed parametric form of the null distribution, GMM was used to adaptively estimate a null distribution from the data to account for unmodeled signal due to physiological noise. Since any distribution can be represented by using a mixture of a sufficient number of Gaussians, separate Gaussian distributions for "activation" and "deactivation" could be identified from each group-level statistical map. All resulting activation and deactivation maps were thresholded at a posterior probability of $p > 0.5$, which corresponds to different z-statistic values for different datasets. Hence, we did not threshold by rejecting the "null" hypothesis, but instead by "accepting" the alternative hypothesis of activation.

Functional connectivity. Functional connectivity analysis for Heat-46 was performed by whole-brain correlation of the average time course extracted from one of two functionally defined networks. Here, functional connectivity reflects temporally correlated neural activity between functionally defined cerebellar networks and spatially remote brain areas. Functional connectivity analysis is fundamentally correlative, and does not necessarily indicate physical connections between structures. Heat-46 activation was spatially divided into: (1) areas exclusively activated by heat (Heat Specific); and (2) areas activated by heat and the contrast between unpleasant and neutral pictures (Heat+$IAPS_{[UNPLS-NEU]}$ Overlap). This division was performed to determine whether heat-related activation in the cerebellum (Heat-46) could be segregated into different functional networks based on overlapping processing of aversive stimuli by a separate modality (vision). These functional networks were transformed from SUIT-space into each subject's native functional space for the Heat-46 scan, and the average Heat-46 time courses for "Heat-specific" and "Heat+$IAPS_{[UNPLS-NEU]}$ Overlap" were calculated for each subject. The preprocessing steps for each subject's functional images were identical to that described above, but with a 5 mm full-width at half-maximum Gaussian filter applied for spatial smoothing of the functional time series, and FLIRT was used to register all subjects' brains into the MNI152 standard brain atlas. The extracted average time courses for Heat-specific and Heat+$IAPS_{[UNPLS-NEU]}$ Overlap were smoothed with a Gaussian kernel whose kernel width was chosen automatically via leave-one-out cross validation. This smoothing was performed to prevent correlations with noise in the raw average time course. GLM analyses were performed using these averaged and smoothed time courses as the regressors using FEAT FILM. The temporal derivative of the time course was not included as an explanatory variable. The results were spatially normalized to MNI152 space, and group analyses were performed with FEAT FLAME to generate separate seed-based GLM maps for Heat-specific and Heat+$IAPS_{[UNPLS-NEU]}$ Overlap. The functional connectivity group analyses results were thresholded as described for the group activation maps.

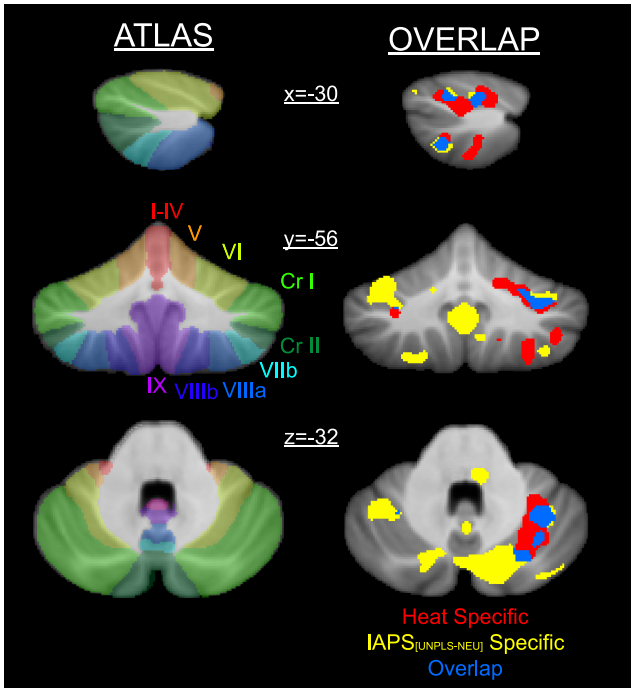

Figure 2. Spatial overlap (blue) of cerebellar responses to noxious heat (red) and Unpleasant-Neutral pictures (yellow) in hemispheric lobules VI, VIIb, and Crus I. The cerebellar lobules on the left are color-coded based on the probabilistic MR atlas of the cerebellum (Diedrichsen et al., 2009). The coordinates displayed correspond to the standard MNI152 atlas. For coronal and axial images, the left cerebellar hemisphere corresponds with the right side of the image. Statistical maps have been spatially smoothed using a median filter for display purposes. CrI, Crus I; CrII, Crus II.

Results

Noxious thermal stimuli

Subjects showed cerebellar activation in response to 46°C stimulation applied to the left hand, which was perceived as painful. Online VAS reports during fMRI scanning indicated that the average pain intensity evoked by 46°C was 6.1 ± 2.5 (SD), while the average unpleasantness was 2.7 ± 2.0 (SD). Significant cerebellar activation was detected predominantly in the left cerebellar hemisphere, with the composition of the largest clusters in lobules VI, Crus I, and VIIb (Fig. 1; Table 1).

Unpleasant pictures

Differential cerebellar responses were found in the $IAPS_{[UNPLS-NEU]}$ contrast. The postscan reports indicated that the average affective valence for the unpleasant pictures was 2.4 ± 1.1 (SD). The unpleasant pictures produced significantly increased activation relative to neutral pictures bilaterally in cerebellar hemispheric lobule VI and Crus I, and in left hemispheric lobules Crus II and VIIb (Fig. 1; Table 2). Spatial overlap of statistical maps for 46°C and $IAPS_{[UNPLS-NEU]}$, also referred to as Heat+$IAPS_{[UNPLS-NEU]}$ Overlap, was detected in the left cerebellar hemispheric lobules VI, Crus I, and VIIb (Fig. 2).

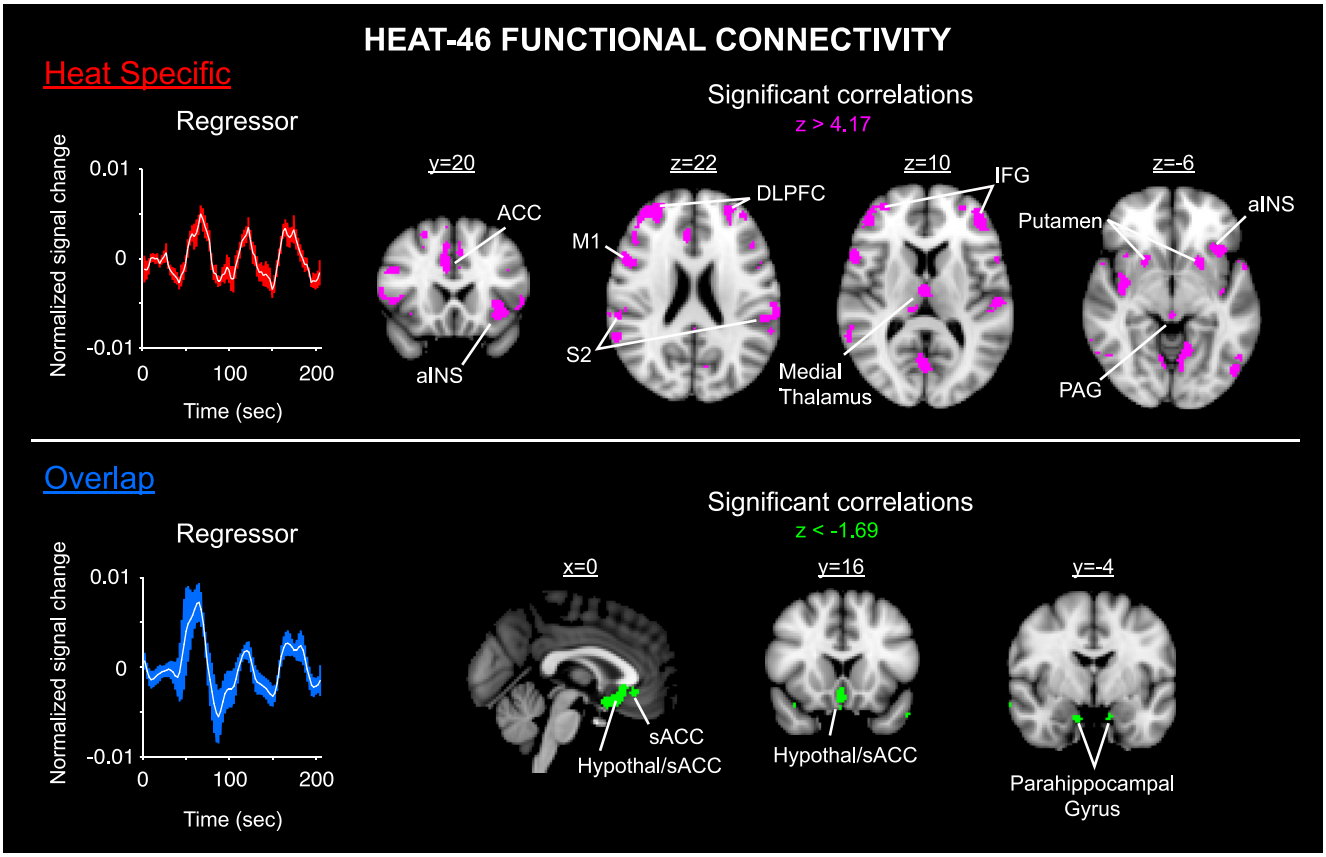

Figure 3. Heat-specific (red) and overlap (blue) cerebellar responses show differential functional connectivity with the rest of the brain. The line graphs show the mean regressor (±SD) used across subjects as extracted from areas identified as heat specific or overlapping (Fig. 2). Normalized signal change was determined using mean-based intensity-normalization of functional time courses for each voxel. The functional connectivity map for the heat-specific areas is depicted in magenta, while the connectivity map for overlap is shown in green. The connectivity maps overlay the standard MNI152 whole-brain atlas. For coronal and axial images, the left cerebral hemisphere corresponds with the right side of the image. Functional connectivity maps were thresholded at a posterior probability of $p > 0.5$ using GMM. Statistical maps have been spatially smoothed using a median filter for display purposes. aINS, Anterior insula; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; Hypothal, hypothalamus; IFG, inferior frontal gyrus; PAG, periaqueductal gray, PHG, parahippocampal gyrus; S2, secondary somatosensory cortex; sACC, subgenual anterior cingulate cortex.

Overlap was also detected in the midbrain (0.25 cm^3), roughly in the location of the right substantia nigra (9, −13, −1).

Heat-specific and Heat+$IAPS_{[UNPLS-NEU]}$ Overlap: functional connectivity

Heat-specific and Heat+$IAPS_{[UNPLS-NEU]}$ Overlap areas in the cerebellum showed different patterns of functional connectivity with the rest of the brain (Fig. 3; Table 3). Heat-specific areas were significantly correlated with brain areas including primary motor cortex, anterior insula, anterior cingulate cortex, secondary somatosensory cortex, medial thalamus, dorsolateral prefrontal cortex, putamen, and the periaqueductal gray. Heat+$IAPS_{[UNPLS-NEU]}$ Overlap areas were significantly inversely correlated with the anterior part of the hypothalamus, subgenual anterior cingulate, and the parahippocampal gyrus.

Pleasant pictures

The $IAPS_{[PLS-NEU]}$ contrast also revealed differential cerebellar responses. The postscan reports indicated that the average affective valence for the pleasant pictures was 7.2 ± 1.0 (SD). Significantly increased activation to pleasant versus neutral pictures was detected primarily in right cerebellar hemispheric lobules VI and Crus II (Table 4), and showed minimal spatial overlap with the areas detected with the $IAPS_{[UNPLS-NEU]}$ contrast (Fig. 4). Pleasant pictures showed decreased activity relative to neutral pictures bilaterally in hemispheric lobule VI.

Discussion

Aversive stimuli in the form of noxious heat and unpleasant pictures activated overlapping areas in the posterior cerebellum, specifically in hemispheric lobules VI, Crus I, and VIIb. Areas that showed spatial overlap with both heat pain and unpleasant picture viewing were significantly inversely correlated with cerebral limbic areas related to emotion, including the hypothalamus, subgenual ACC, and the parahippocampal gyrus. These inverse correlations suggest that activation in the posterior cerebellum is associated with decreased activation in a limbic network for emotional processing. Heat-specific functional connectivity was detected in many pain-related and sensorimotor structures, including M1, S2, anterior insula, and the periaqueductal gray, supporting an interaction of brain systems involved in noxious thermosensory and motor processing. Specifically, the separate cortical networks suggest that noxious heat-evoked responses in the cerebellum can be divided into sensorimotor and emotional networks (Fig. 5). We also observed an apparent distinction in the spatial localization of unpleasant and pleasant pictures. Identification of an aversive emotional network that includes the cerebellum has potential ramifications for our understanding of multimodal associative learning.

Table 3. Cerebral functional connectivity of cerebellar regions that were heat specific, and those that had overlapping responses to noxious heat and the unpleasant-neutral picture contrast

Brain region	MNI (z_{max}) Side	*x*	*y*	*z*	*z*-stat	Vol (cm^3)
Heat specific—positive correlations ($z > 4.17$)[a]						
Cingulum						
ACC	M	2	6	40	5.64	21.85
PCC	M	2	−18	44	5.24	2.50
	M	0	−14	40	5.24	1.07
Insula						
Anterior	R	58	14	2	5.56	6.00
	R	56	14	−2	5.38	0.73
Frontal						
Frontal pole	L	−32	54	22	5.51	16.19
	R	32	52	22	5.33	21.04
M1	R	40	−20	52	5.47	7.48
	R	30	−10	52	5.40	6.06
SFG	R	16	0	62	5.36	1.76
	R	14	4	62	5.28	1.50
Subcortical						
Thalamus	R	14	−24	10	5.46	0.62
	L	−10	−20	2	5.35	1.70
	L	−14	−18	6	5.31	2.18
	R	16	−20	12	5.31	0.36
Putamen	R	24	10	−2	5.29	11.26
PAG	B	10	−32	−6	5.24	9.77
Parietal						
S2	L	−60	−30	16	5.31	29.86
SMG	R	52	−36	46	5.31	7.12
	R	56	−24	40	5.27	2.82
	R	60	−30	32	5.25	10.85
Occipital						
Lateral	R	34	−62	48	5.26	9.13
Overlap—negative correlations ($z < -1.69$)[b]						
Cingulum						
sACC	M	0	26	−4	−3.88	0.31
	M	−2	26	−8	−3.57	0.30
Subcortical						
Hypothalamus	M	2	16	−14	−3.53	2.63
	M	−2	20	−6	−3.19	0.32
Temporal						
PHG	R	18	−6	−24	−3.53	0.60
	L	−12	−4	−28	−3.01	0.23
	R	18	4	−30	−3.07	0.34
TP	L	−46	22	−22	−3.03	0.37
Parietal						
S1	L	−64	−10	30	−2.83	0.31

Note: Thresholds were determined using Gaussian Mixture Modeling (Pendse et al., 2009). Minimum 7 voxels in acquired space (0.30 cm^3). L, Left; R, right; M, midline; ACC, anterior cingulate cortex; M1, primary motor cortex; PAG, periaqueductal gray; PCC, posterior cingulate cortex; PHG, parahippocampal gyrus; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; sACC, subgenual anterior cingulate; SFG, superior frontal gyrus; SMG, supramarginal gyrus; TP, temporal pole.

[a]Max *z*-stat.

[b]Min *z*-stat.

Table 4. Differential cerebellar responses to pleasant and neutral images

Cluster	Max ROI	MNI (z_{max}) *x*	*y*	*z*	Max *z*-stat	Vol (mm^3)	Composition
Contrast analysis—IAPS: Pls>Neu ($z > 1.24$)							
1	R VI	34	−41	−37	1.76	0.33	81% R VI; 7% R CrI; 5% R V
2	R CrI	47	−65	−44	1.61	0.30	66% R CrII; 31% R CrI
Contrast analysis—IAPS: Pls<Neu ($z > 0.95$)							
1	R VI	28	−68	−22	2.72	1.48	81% R VI; 10% R CrI
2	L CrI	−30	−79	−25	2.71	6.96	57% L VI; 28% L CrI; 4% L V
3	R VI	33	−60	−24	2.58	2.55	70% R VI; 15% R V; 4% R CrI
4	R VI	12	−77	−21	2.50	1.58	64% R VI; 25% R CrI; 5% Vermis VI
5	R CrI	24	−76	−24	2.50	0.55	51% R CrI; 44% R VI
6	R CrI	34	−75	−25	2.27	0.66	96% R CrI; 1% R VI

Thresholds were determined using Gaussian mixture modeling (Pendse et al., 2009). Cerebellar regions were identified using the SUIT probabilistic atlas of the human cerebellum (Diedrichsen et al., 2009). Minimum 7 voxels in acquired space (300 mm^3). L, Left; R, right; CrI, Crus I; CrII, Crus II.

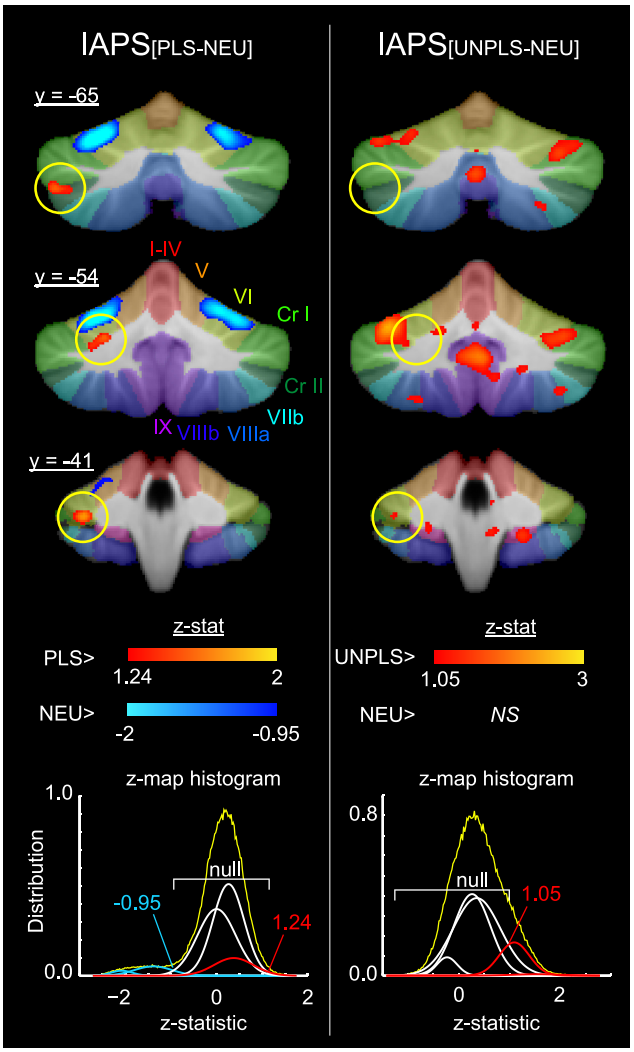

Figure 4. Cerebellar responses to Pleasant-Neutral pictures spatially differ from responses to Unpleasant-Neutral pictures. Yellow circles highlight the location of clusters of significantly increased activation with Pleasant-Neutral pictures. The statistical maps overlay the SUIT atlas, and the coordinates displayed correspond to the standard MNI152 atlas. For coronal and axial images, the left cerebellar hemisphere corresponds with the right side of the image. Activation and deactivation maps were thresholded at a posterior probability of $p > 0.5$ using GMM. Statistical maps have been spatially smoothed using a median filter for display purposes. *Z*-map histograms show the positive (red) and negative (blue) distributions relative to the null distribution (white) identified by Gaussian mixture modeling of the *z*-statistic histograms (yellow) for Pleasant-Neutral and Unpleasant-Neutral contrasts. The colored numbers indicate the *z*-statistic thresholds determined by differentiation of positive and negative distributions from the null. CrI, Crus I; CrII, Crus II.

A meta-analysis based on activation likelihood estimates of neuroimaging studies indicates that lobule VI, Crus I, and VIIb may relate to processing of emotion and executive functions (Stoodley and Schmahmann, 2009). The emotion condition as defined in the meta-analysis is similar to our IAPS task, as eight of the nine included studies used pictures to evoke emotion, including six that used IAPS. Within-subject analyses indicate that these cerebellar areas activate with noxious heat similarly to that observed with passive viewing of unpleasant IAPS pictures. The precise topography of cerebellar activation across different domains of executive function still remains to be shown.

We propose the existence of a corticocerebellar network relating to aversive stimuli, as cerebellar areas commonly activated by noxious heat and unpleasant pictures showed functional connectivity with brain structures that are associated with emotional processing, specifically the subgenual ACC, hypothalamus, and parahippocampal gyrus (Papez, 1937; Reiman et al., 1997). The contrast between pleasant and neutral pictures did not significantly affect the same cerebellar areas as observed with the aversive stimuli, suggesting that their participation in this emotional network is preferential to negatively valenced stimuli. The processing of negative affect has previously been related to each of these limbic structures: sadness is associated with subgenual ACC (Mayberg et al., 1999; Vogt, 2005) and hypothalamic activation (Karlsson et al., 2010); and parahippocampal gyrus activation is associated with the amplification of pain by anxiety (Ploghaus et al., 2001). The link between the cerebellum and the limbic system suggests a functional pathway for the cerebellum's role in emotional processing (Heath, 1977; Schmahmann, 1991; Murphy et al., 2003; Konarski et al., 2005; Fusar-Poli et al., 2009).

The hypothalamus, subgenual ACC, and hippocampus, the areas inversely correlated with this cerebellar aversion network, show similar disengagement with descending modulatory systems during "circa-strike" defensive contexts associated with predatory attack in humans (Mobbs et al., 2009). Aversive-related areas in the cerebellum may be related to circa-strike decreases observed in the cortex, and may reflect a disengagement process during aversive stimuli. Drawing from classical animal literature, electrophysiological recordings in the cat suggest that direct electrical stimulation of the cerebellum has a similarly suppressive effect on structures within the Circuit of Papez (Snider and Maiti, 1976). We propose that the inverse correlations we observed between the cerebellum and the limbic system represent cerebellar modulation in the processing of negative affect. Perhaps the cerebellar aversive-related responses are part of a defensive fear system, which are often studied in the context of classical conditioning models.

In classical conditioning, the cerebellum plays a key role in the acquisition of both motor and non-motor unconditioned responses (Lincoln et al., 1982; Bellebaum and Daum, 2011). In patients with cerebellar dysfunction, eyeblink classical conditioning is often impaired (Daum et al., 1993; Topka et al., 1993; Gerwig et al., 2003, 2007). The most commonly afflicted cerebellar areas in patients with deficiencies in associative learning are hemispheric lobule VI and Crus I ipsilateral to the lesion (Gerwig et al., 2003). Though not as thoroughly examined as the eyeblink motor-learning model, the cerebellum is also important in multimodal associative learning (Drepper et al., 1999; Timmann et al., 2010) and has also been suggested to occur in hemispheric lobule VI (Bellebaum and Daum, 2011). Note that both lobule VI and Crus I were active during noxious heat, and showed increased activation in the unpleasant versus neutral pictures contrast. This suggests that the cerebellum may similarly process heat pain and unpleasant pictures as aversive stimuli in the context of associative learning. This is also suggested by the functional connectivity that these areas share with the subgenual ACC and the hippocampal complex, which are both associated with conditioning (Büchel et al., 1999; Phelps et al., 2004). The concept of a generalized aversive encoding of pain in the cerebellum may explain similar cerebellar activation in studies of pain anticipation (Ploghaus et al., 1999) as well as pain empathy (Singer et al., 2004), as these phenomena are both aversive experiences without physical stimuli.

A growing body of literature supports a cognitive and/or emotional role for the cerebellum in addition to its classical role in motor processing (Strick et al., 2009; Wolf et al., 2009; Murdoch, 2010; Schmahmann, 2010; Timmann and Daum, 2010). Neuro-

anatomically, the cerebellum is interconnected with the limbic system, along with the frontal and parietal associative areas (Middleton and Strick, 1994; Schmahmann and Pandya, 1997; Kelly and Strick, 2003). At the neurochemical level, cerebellar function is directly regulated by dopamine, serotonin, and norepinephrine (Dieudonné, 2001; Schweighofer et al., 2004; Giompres and Delis, 2005), the most extensively investigated neurotransmitters in the literature on reward motivation and emotions (Charney, 2004). From a clinical perspective, in addition to the high prevalence of thought disorders and negative affect states in patients with cerebellar lesions (Schmahmann and Sherman, 1998; Wolf et al., 2009), patients with mood, anxiety, psychotic, and attention deficit disorders consistently display prominent cerebellar dysfunctions (Andreasen et al., 1998; Brambilla et al., 2002; Roth and Saykin, 2004; Liu et al., 2010; Nakao et al., 2011). Our study suggests that investigations of emotional processing in the cerebellum are not limited to inferences made in clinical populations, but can also be studied in healthy human subjects.

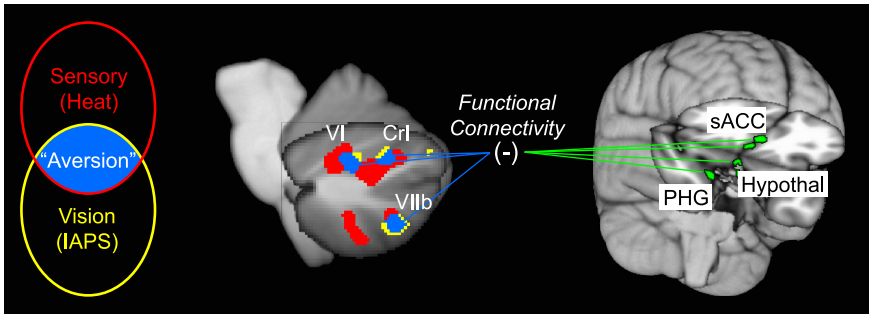

Figure 5. Schematic model of the putative heat-specific and aversion cerebellar-cortical networks. Multimodal aversive responses to sensory and visual stimuli were evoked in the cerebellum. With noxious heat, responses were divided into heat-specific (red) and aversive cerebellar networks (blue), based on the spatial overlap with the contrast of unpleasant versus neutral pictures (yellow). Functional connectivity analysis in the noxious heat scan revealed that these aversive cerebellar networks were negatively correlated with areas previously related to emotional processing (green). CrI, Crus I; Hypothal, hypothalamus; PHG, parahippocampal gyrus; sACC, subgenual anterior cingulate cortex.

Caveats

An alternative explanation for lobule VI and Crus I activation may relate to the processing of visual selective attention. A previous neuroimaging study dissociated motor- versus attention-related activation in the cerebellum (Allen et al., 1997), with attention activating the posterior part of the quadrangular (lobule VI) and the superior part of the semilunar lobule (Crus I). The authors suggested that attention-related activation relates to the acquisition of new sensory information and linking it with an appropriate anticipatory operation, whether cognitive or motor. Although those authors had interpreted activation during attention as a learning-related operation, the possibility that these cerebellar areas could reflect attention should be considered in the context of our results. We make the case that in our experiment, lobule VI and Crus I activation do not reflect attention because: (1) attention was controlled to some degree in the "unpleasant versus neutral" contrast; and (2) the "pleasant versus neutral" contrast did not show the same differential activation as unpleasant versus neutral in these areas, whereas an attentional process might be presumed to act similarly regardless of stimulus valence.

Several additional caveats should be considered in light of these findings. Though noxious heat and unpleasant pictures activate similar cerebellar areas, these stimuli may evoke shared processes aside from aversion. These could include visceromotor reflexes, inner speech, and involuntary facial expressions. Furthermore, prolonged exposure to unpleasant IAPS pictures can induce a short-term mood state, characterized by enhanced startle reactions and frowning (Smith et al., 2005). Additional experiments will be necessary to explore the contributions of these possible influences, as well as the likelihood that this putative cerebellar aversion-circuitry responds to additional sensory modalities (Small et al., 2003).

Conclusions

This study suggests the existence of a corticocerebellar aversive network that includes the posterior cerebellar hemispheres, parahippocampal gyrus, and basal forebrain structures. These findings hold mechanistic implications for patients suffering from strokes localized to the posterior cerebellum (Schmahmann and Sherman, 1998; Exner et al., 2004) or who have their cerebellum lesioned at an early age (Levisohn et al., 2000; Riva and Giorgi, 2000). The cerebellum's role as modulator of limbic systems indicates that it may restrain sensitivity to stressful/aversive events, and may be a marker for vulnerability to the development of stress-related disorders. This study provides a new perspective toward the role of the cerebellum during pain processing as it relates to aversion, and adds to the growing evidence of cerebellar participation in non-motor processes.

References

Allen G, Buxton RB, Wong EC, Courchesne E (1997) Attentional activation of the cerebellum independent of motor involvement. Science 275:1940–1943.

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, text revision (DSM-IV-TR), Ed 4. Washington, DC: American Psychiatric Association, Inc.

Anderson KO, Syrjala KL, Cleeland CS (2001) How to assess cancer pain. In: Handbook of pain assessment (Turk DC, Melzack R, eds), pp 579–600. New York: Guilford.

Andreasen NC, Paradiso S, O'Leary DS (1998) "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr Bull 24:203–218.

Ashburner J, Friston KJ (1999) Nonlinear spatial normalization using basis functions. Hum Brain Mapp 7:254–266.

Bellebaum C, Daum I (2011) Mechanisms of cerebellar involvement in associative learning. Cortex 47:128–136.

Bermpohl F, Pascual-Leone A, Amedi A, Merabet LB, Fregni F, Gaab N, Alsop D, Schlaug G, Northoff G (2006) Dissociable networks for the expectancy and perception of emotional stimuli in the human brain. Neuroimage 30:588–600.

Bingel U, Quante M, Knab R, Bromm B, Weiller C, Büchel C (2002) Subcortical structures involved in pain processing: evidence from single-trial fMRI. Pain 99:313–321.

Borsook D, Moulton EA, Tully S, Schmahmann JD, Becerra L (2008) Human cerebellar responses to brush and heat stimuli in healthy and neuropathic pain subjects. Cerebellum 7:252–272.

Brambilla P, Barale F, Caverzasi E, Soares JC (2002) Anatomical MRI findings in mood and anxiety disorders. Epidemiol Psychiatr Soc 11:88–99.

Büchel C, Dolan RJ, Armony JL, Friston KJ (1999) Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. J Neurosci 19:10869–10876.

Casey KL, Minoshima S, Morrow TJ, Koeppe RA (1996) Comparison of human cerebral activation pattern during cutaneous warmth, heat pain, and deep cold pain. J Neurophysiol 76:571–581.

Charney DS (2004) Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. Am J Psychiatry 161:195–216.

Daum I, Schugens MM, Ackermann H, Lutzenberger W, Dichgans J, Birbaumer N (1993) Classical conditioning after cerebellar lesions in humans. Behav Neurosci 107:748–756.

Diedrichsen J (2006) A spatially unbiased atlas template of the human cerebellum. Neuroimage 33:127–138.

Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N (2009) A probabilistic MR atlas of the human cerebellum. Neuroimage 46:39–46.

Dieudonné S (2001) Serotonergic neuromodulation in the cerebellar cortex: cellular, synaptic, and molecular basis. Neuroscientist 7:207–219.

Drepper J, Timmann D, Kolb FP, Diener HC (1999) Non-motor associative learning in patients with isolated degenerative cerebellar disease. Brain 122:87–97.

Exner C, Weniger G, Irle E (2004) Cerebellar lesions in the PICA but not SCA territory impair cognition. Neurology 63:2132–2135.

Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, Benedetti F, Abbamonte M, Gasparotti R, Barale F, Perez J, McGuire P, Politi P (2009) Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 34:418–432.

Gerwig M, Dimitrova A, Kolb FP, Maschke M, Brol B, Kunnel A, Böring D, Thilmann AF, Forsting M, Diener HC, Timmann D (2003) Comparison of eyeblink conditioning in patients with superior and posterior inferior cerebellar lesions. Brain 126:71–94.

Gerwig M, Kolb FP, Timmann D (2007) The involvement of the human cerebellum in eyeblink conditioning. Cerebellum 6:38–57.

Giompres P, Delis F (2005) Dopamine transporters in the cerebellum of mutant mice. Cerebellum 4:105–111.

Heath RG (1977) Modulation of emotion with a brain pacemaker. Treatment for intractable psychiatric illness. J Nerv Ment Dis 165:300–317.

Helmchen C, Mohr C, Erdmann C, Petersen D, Nitschke MF (2003) Differential cerebellar activation related to perceived pain intensity during noxious thermal stimulation in humans: a functional magnetic resonance imaging study. Neurosci Lett 335:202–206.

Karlsson KA, Windischberger C, Gerstl F, Mayr W, Siegel JM, Moser E (2010) Modulation of hypothalamus and amygdalar activation levels with stimulus valence. Neuroimage 51:324–328.

Kelly RM, Strick PL (2003) Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J Neurosci 23:8432–8444.

Konarski JZ, McIntyre RS, Grupp LA, Kennedy SH (2005) Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? J Psychiatry Neurosci 30:178–186.

Lane RD, Reiman EM, Bradley MM, Lang PJ, Ahern GL, Davidson RJ, Schwartz GE (1997) Neuroanatomical correlates of pleasant and unpleasant emotion. Neuropsychologia 35:1437–1444.

Lang PJ, Bradley MM, Cuthbert BN (2008) International affective picture system (IAPS): affective ratings of pictures and instruction manual. Gainesville, FL: University of Florida.

Levisohn L, Cronin-Golomb A, Schmahmann JD (2000) Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. Brain 123:1041–1050.

Lincoln JS, McCormick DA, Thompson RF (1982) Ipsilateral cerebellar lesions prevent learning of the classically conditioned nictitating membrane/eyelid response. Brain Res 242:190–193.

Liu Z, Xu C, Xu Y, Wang Y, Zhao B, Lv Y, Cao X, Zhang K, Du C (2010) Decreased regional homogeneity in insula and cerebellum: a resting-state fMRI study in patients with major depression and subjects at high risk for major depression. Psychiatry Res 182:211–215.

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT (1999) Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry 156:675–682.

Middleton FA, Strick PL (1994) Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science 266:458–461.

Mobbs D, Marchant JL, Hassabis D, Seymour B, Tan G, Gray M, Petrovic P, Dolan RJ, Frith CD (2009) From threat to fear: the neural organization of defensive fear systems in humans. J Neurosci 29:12236–12243.

Moulton EA, Schmahmann JD, Becerra L, Borsook D (2010) The cerebellum and pain: passive integrator or active participator? Brain Res Rev 65:14–27.

Murdoch BE (2010) The cerebellum and language: historical perspective and review. Cortex 46:858–868.

Murphy FC, Nimmo-Smith I, Lawrence AD (2003) Functional neuroanatomy of emotions: a meta-analysis. Cogn Affect Behav Neurosci 3:207–233.

Nakao T, Sanematsu H, Yoshiura T, Togao O, Murayama K, Tomita M, Masuda Y, Kanba S (2011) fMRI of patients with social anxiety disorder during a social situation task. Neurosci Res 69:67–72.

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113.

Papez JW (1937) A proposed mechanism of emotion. Arch Neurol Psychiatry 38:725–744.

Paradiso S, Johnson DL, Andreasen NC, O'Leary DS, Watkins GL, Ponto LL, Hichwa RD (1999) Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. Am J Psychiatry 156:1618–1629.

Pendse G, Borsook D, Becerra L (2009) Enhanced false discovery rate using Gaussian mixture models for thresholding fMRI statistical maps. Neuroimage 47:231–261.

Peyron R, Laurent B, Garcia-Larrea L (2000) Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin 30:263–288.

Phelps EA, Delgado MR, Nearing KI, LeDoux JE (2004) Extinction learning in humans: role of the amygdala and vmPFC. Neuron 43:897–905.

Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, Rawlins JN (1999) Dissociating pain from its anticipation in the human brain. Science 284:1979–1981.

Ploghaus A, Tracey I, Clare S, Gati JS, Rawlins JN, Matthews PM (2000) Learning about pain: the neural substrate of the prediction error for aversive events. Proc Natl Acad Sci U S A 97:9281–9286.

Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PM, Rawlins JN, Tracey I (2001) Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci 21:9896–9903.

Reiman EM, Lane RD, Ahern GL, Schwartz GE, Davidson RJ, Friston KJ, Yun LS, Chen K (1997) Neuroanatomical correlates of externally and internally generated human emotion. Am J Psychiatry 154:918–925.

Riva D, Giorgi C (2000) The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. Brain 123:1051–1061.

Roth RM, Saykin AJ (2004) Executive dysfunction in attention-deficit/hyperactivity disorder: cognitive and neuroimaging findings. Psychiatr Clin North Am 27:83–96.

Schmahmann JD (1991) An emerging concept. The cerebellar contribution to higher function. Arch Neurol 48:1178–1187.

Schmahmann JD (2010) The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. Neuropsychol Rev 20:236–260.

Schmahmann JD, Pandya DN (1997) The cerebrocerebellar system. Int Rev Neurobiol 41:31–60.

Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome. Brain 121:561–579.

Schweighofer N, Doya K, Kuroda S (2004) Cerebellar aminergic neuromodulation: towards a functional understanding. Brain Res Brain Res Rev 44:103–116.

Seymour GE (1976) The structure and predictive ability of the Cornell Medical Index for a normal sample. J Psychosom Res 20:469–478.

Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD (2004) Empathy for pain involves the affective but not sensory components of pain. Science 303:1157–1162.

Small DM, Gregory MD, Mak YE, Gitelman D, Mesulam MM, Parrish T (2003) Dissociation of neural representation of intensity and affective valuation in human gustation. Neuron 39:701–711.

Smith JC, Bradley MM, Lang PJ (2005) State anxiety and affective physiology: effects of sustained exposure to affective pictures. Biol Psychol 69:247–260.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 [Suppl 1]:S208–S219.

Snider RS, Maiti A (1976) Cerebellar contributions to the Papez circuit. J Neurosci Res 2:133–146.

Stoodley CJ, Schmahmann JD (2009) Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage 44:489–501.

Strick PL, Dum RP, Fiez JA (2009) Cerebellum and nonmotor function. Annu Rev Neurosci 32:413–434.

Strigo IA, Duncan GH, Boivin M, Bushnell MC (2003) Differentiation of visceral and cutaneous pain in the human brain. J Neurophysiol 89:3294–3303.

Timmann D, Daum I (2010) How consistent are cognitive impairments in patients with cerebellar disorders? Behav Neurol 23:81–100.

Timmann D, Drepper J, Frings M, Maschke M, Richter S, Gerwig M, Kolb FP (2010) The human cerebellum contributes to motor, emotional and cognitive associative learning. A review. Cortex 46:845–857.

Topka H, Valls-Sole J, Massaquoi SG, Hallett M (1993) Deficit in classical conditioning in patients with cerebellar degeneration. Brain 116:961–969.

Vogt BA (2005) Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci 6:533–544.

Wolf U, Rapoport MJ, Schweizer TA (2009) Evaluating the affective component of the cerebellar cognitive affective syndrome. J Neuropsychiatry Clin Neurosci 21:245–253.

Woolrich MW, Ripley BD, Brady M, Smith SM (2001) Temporal autocorrelation in univariate linear modeling of FMRI data. Neuroimage 14:1370–1386.

Yelle MD, Oshiro Y, Kraft RA, Coghill RC (2009) Temporal filtering of nociceptive information by dynamic activation of endogenous pain modulatory systems. J Neurosci 29:10264–10271.